August 2, 2007

Ken Nitschke
EH&S Toxicology & Environmental Research & Consulting
The Dow Chemical Company
1691 North Swede
Building 1803
Midland, MI 48674

Dear Mr. Nitschke:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for 3-Cyclohexene-1-carboxylic acid, 3-cyclohexen-1-ylmethyl ester (Diene 221), posted on the ChemRTK HPV Challenge Program Web site on February 3, 2006. I commend The Dow Chemical Company for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Dow Chemical advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact me at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

Mark W. Townsend, Chief
HPV Chemicals Branch

Enclosure

cc: O. Hernandez
N. Patel
J. Willis

EPA Comments on Chemical RTK HPV Challenge Submission:
3-Cyclohexene-1-carboxylic acid, 3-cyclohexen-1-ylmethyl ester (Diene 221)

Summary of EPA Comments

The sponsor, the Dow Chemical Company, submitted the test plan and robust summaries to EPA for 3-cyclohexene-1-carboxylic acid, 3-cyclohexen-1-ylmethyl ester (Diene 221; CAS No. 2611-00-9) dated December 22, 2005. Data were also provided for the proposed supporting substance tetrahydrobenzaldehyde (THBA, CAS No. 100-50-5). EPA posted the submission on the Chemical RTK HPV Challenge Web site on February 3, 2006.

EPA has reviewed the submission and has reached the following conclusions:

1. Supporting substance. THBA does not support the biodegradation or ecotoxicity endpoints. The use of THBA to support the health effects endpoints is speculative and inconclusive as submitted. The justification lacks experimental support and is not adequately documented. A more detailed and documented analysis may justify the use of this supporting chemical.

2. Physicochemical Properties. EPA agrees with the submitter's proposal to test for all the physicochemical property endpoints. The submitter needs to address some discrepancies in the test plan and robust summaries.

3. Environmental Fate. The submitter needs to address some discrepancies among the stability-in-water values presented in the test plan and robust summaries. The submitter needs to provide measured ready biodegradation data.

4. Health Effects. The submitter claimed exemption from reproductive effects testing on the basis of closed system intermediate (CSI) status. EPA agrees that Diene 221 qualifies for reduced testing for the purposes of the HPV Challenge Program and that data are thus not needed for the repeated-dose and reproductive toxicity endpoints. However, the submitter needs to provide data for the developmental toxicity endpoint. EPA reserves judgment on using the THBA data submitted for the genetic toxicity endpoints pending the submission of a stronger justification.

5. Ecological Effects. The submitter needs to provide data for all aquatic toxicity endpoints.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the Diene 221 Challenge Submission

Test Plan

Supporting Substance Justification

The proposed supporting substance, THBA, is an expected intermediate metabolite of Diene 221.

THBA is not an appropriate data source for the biodegradation or ecotoxicity endpoints (see those sections below). For the health effects endpoints, the proposed metabolic transformation of the sponsored substance is reasonable. However, the submitter needs to better support the proposed "rapid" metabolism of Diene 221 to predominantly THBA and tetrahydrobenzoic acid with more quantitative data on Diene 221 or similar esters.

THBA is itself a sponsored substance under the HPV Challenge Program. EPA comments on that submission (http://www.epa.gov/chemrtk/pubs/summaries/tetrahyb/c15755tc.htm) should be considered in conjunction with those outlined for Diene 221.

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility)

On page 7 of the test plan, the submitter indicates that they would provide measured data to replace the calculated data for all physicochemical endpoints because the sponsored substance is a liquid at room temperature (25 □C) whereas the estimated value for melting point is 46.9 □C (reported in the robust summary, and in table 2 of the test plan). Although EPA agrees with the submitter's intent, in table 8 of the test plan, the submitter provides a melting point value of -66 □C and indicates that this endpoint has adequate existing data.

The submitter provides a boiling point value of 276 □C in Table 8 of the test plan, indicating that this endpoint has adequate existing data. Table 2 provides a calculated value of 299 □C, and in the robust summary, Section 2.2 (boiling point) has no data entered.

The submitter needs to address discrepancies and provide consistent values in all documents.

In order to provide adequate physicochemical property data, the submitter needs to follow OECD TG 102 (melting point), 103 (boiling point), 104 (vapor pressure), 107 or 117 (Partition Coefficient (n-octanol/water), and 105 (water solubility).

Environmental Fate (photodegradation, stability in water, biodegradation, and fugacity)

The data provided by the submitter for photodegradation are adequate for the purposes of the HPV Challenge Program. EPA agrees with the submitter's plan to recalculate the fugacity using the measured physicochemical values.

Stability in water. On page 7 of the test plan, the submitter indicates that "the model predicts Diene 221 will slowly hydrolyze" and in table 3 it indicates that Diene 221 has a calculated half life of 9.2 years at 25 □C and pH 7. However, in table 8, the submitter incorrectly reports that Diene 221 "does not contain hydrolysable groups" and that this endpoint requirement is satisfied with adequate existing data, while Section 3.1.2 (Stability in water) in the robust summary contains no data. The submitter needs to clarify these discrepancies and provide consistent values in all documents.

Biodegradation. The submitter states in Table 1 of the test plan that there are sufficient data for this endpoint on the basis of calculated data for Diene 221 using BIOWIN and measured data for tetrahydrobenzaldehyde (THBA). Calculated biodegradation values generally are not adequate for the purposes of the HPV Challenge Program, and THBA data are not adequate for Diene 221 for the biodegradation endpoint owing to the differences in structure and reactivity. The submitter needs to provide measured ready biodegradation data for Diene 221 following OECD TG 301.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/ developmental toxicity)

Adequate data were provided for the acute toxicity endpoint. EPA reserves judgment on the data provided for the genetic toxicity endpoints pending the receipt of a stronger justification for using THBA data. Performing the two *in vitro* tests on the sponsored substance may be a better alternative than attempting to support the use of THBA with adequate pharmacokinetic and other data.

Repeated-dose/reproductive/developmental toxicity. Data for the reproductive and developmental toxicity endpoints are inadequate for the sponsored substance and the proposed supporting chemical. No data were submitted for the developmental toxicity endpoint. While in its comments on THBA (http://www.epa.gov/chemrtk/pubs/summaries/tetrahyb/c15755tc.htm) EPA waived the need to test for the reproductive/developmental toxicity endpoints because of the available repeated-dose toxicity data and THBA's corrosive nature, Diene 221 is not considered corrosive, and no metabolic profiling data were submitted to support the claimed rapid metabolism to THBA; thus, adequate data are not available for these three endpoints.

The submitter states that "since Diene 221 is a closed system intermediate there is no need for a reproduction study." The Guidance for Testing Closed System Intermediates for the HPV Challenge Program (http://www.epa.gov/chemrtk/pubs/general/closed9.htm) allows for a reduced testing rationale provided certain criteria are met. The information required to judge a "closed system intermediate" claim must address the following:

I. Site information.
   A. Number of sites.
   B. Basis for "closed process" conclusion at each site.
      1) Process description.
      2) Monitoring data showing no detection.
      3) In the absence of monitoring data, the basis for believing that releases do not occur.
   C. Data on "presence in distributed products"

II. Information on transport (mode, volume, controls, etc.)

III. A data search showing that the chemical is not present in other end-products."

EPA agrees that the submitter has adequately addressed the criteria above. Diene 221 is produced at a single site, is consumed in the in-process reaction to make the final product, and there are no off-site shipments. Available data indicate that Diene 221 is present in end-products at less than 1 ppm. Therefore, *testing is not needed for the repeated-dose and reproductive toxicity endpoints*.

However, the submitter does need to provide data for the developmental toxicity endpoint for the sponsored substance for the purposes of the HPV Challenge Program, preferably according to OECD TG 421.

Ecological Effects (fish, invertebrate, and algae)

EPA disagrees with the submitter that the predicted data submitted are adequate for the aquatic toxicity endpoints. Nor is the proposed use of THBA data suitable for these endpoints; EPA has addressed the issue of ester metabolism in the ecotoxicity context in comments on earlier submissions (http://www.epa.gov/chemrtk/pubs/summaries/terprial/c12965tc.htm, http://www.epa.gov/chemrtk/pubs/summaries/tertestr/c12930tc.htm). The submitter needs to provide adequate data for the fish, invertebrate and algae toxicity endpoints according to OECD TG 203, 202 and 201 respectively. ECOSAR predictions may be submitted if accompanied by suitable analog data.

Specific Comments on Robust Summaries

None.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.